The congress aimed at challenging animal experiments as the gold standard and addressed the public, academics, and regulators. Simultaneous translation was provided. Guests included numerous scientists, representatives of authorities, politicians, veterinarians, and physicians as well as interested persons from the animal protection movement and the public. WIST II was very well received by the participants and certainly helped to further stimulate the discussion about the validity of animal experiments.

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Meeting Report

Alternative Methods to Replace or Reduce Animal Models in Biomedical Research

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The first open meeting of the R2N consortium, Replace and Reduce (R2N) based in Lower Saxony, on alternative methods to replace or reduce animal experiments took place at the Hannover Medical School (MHH), in Hannover, Germany on November 6-7, 2018. The meeting was chaired by Prof. **André Bleich** (Director of the Central Animal Facility and Institute for Animal Sciences, MHH) and Prof. **Nils Hope** (Centre for Ethics and Law in the Life Sciences, Leibniz University Hannover). The gathering aimed to discuss the latest technologies and opportunities to replace and reduce animal testing as well as to encourage scientific exchange among industry, academia, and students. The meeting was opened by Prof. André Bleich, who highlighted the relevance of alternatives to animal experiments in all areas of biomedical science in order to reduce the number of animals used in research, and stated that such approaches are leading the science into a new era.

Prof. **Thomas Hartung** (Johns Hopkins Centre for Alternatives to Animal Testing, Baltimore, MD, USA) stressed the increasing need for more representative tests to predict human health threats. Given the limitations of animal-based toxicology and traditional human cell culture, the combination of the biomedical and bioengineering fields is the key to produce more reliable methods that better emulate the human *in vivo* environment. One of the solutions to testing the reaction of brain cells to foreign substances is the human iPSC-derived mini-brain. Another measure to reduce animal testing in toxicology is the software tool REACH*Across*™, which uses a large toxicological database (an *in silico* method) to predict the effects of substances based on chemical similarity to substances that have been characterized.

Dr **Sylvia Escher** (Fraunhofer ITEM, Hannover, Germany) presented the development of an animal-free testing strategy for risk assessment of inhalable compounds. The project "EXITOX II" develops an integrated approach for testing and assessment (IATA) of compounds which combines the outcomes of *in vitro*, *ex vivo*, and *in silico* models. The project also has developed two *in silico* models, i.e., a lung-PBPK (physiologically based pharmacokinetic) model that predicts the uptake and distribution of volatile chemicals in the human respiratory tract and a QSAR model that predicts plasma protein binding, an important input parameter for PBPK modelling. Both tools will be available for use in the near future for quantitative *in vitro* to *in vivo* extrapolation (IVIVE).

To overcome the limitations of single cell culture and the use of non-human species for testing of drug candidates, **Isabel Rütschle** (TissUse GmbH, Berlin, DE) presented the organ-on-a-chip model. Such chips are roughly the size of a credit card and house miniaturized organs. The system allows interactions between different organs via a microfluidic system driven by a peristaltic pump. Multi-organ-chips are being developed to replace animal use for pre-clinical testing of drugs as well as toxicological testing of cosmetic ingredients and chemicals. They can be used to model physiological and pathophysiological conditions, e.g., Type II diabetes and Alzheimer's disease.

PD Dr **Alexander Mosig** (University Hospital Jena, Jena, DE) introduced the *in vitro* gut-liver axis model. The system aims to investigate molecular and cellular mechanisms of inflammation-associated organ dysfunction in sepsis. To date, there is no specific anti-sepsis drug and the sepsis treatment relies mainly on early detection and symptomatic approaches. The *in vitro* gut-liver axis model is composed of parenchymal as well as circulating immune cells. Acute and chronic infection models are established to permit study of sepsis-associated multi-organ failure *in vitro*. The system has potential to reduce the number of experimental animals used for the study of sepsis.

Demonstrating the applicability of stem cell models developed in academia to pharmaceutical environments, Dr **Udo Kraushaar** (Natural and Medical Sciences Institute at the University of Tübingen, Tübingen, Germany) presented cell culture models of hiPS cardiomyocytes and neurons. Methods to differentiate somatic cells from human embryonic stem cells (hESC) and human induced pluripotent stem cells (hiPSC) now allow the use of human cellular material for compound screening and

drug validation. Examples were given of how the drug discovery field exploits this opportunity (e.g., the CiPA initiative) and of the current endeavours to develop and validate new assays in order to increase the predictive power and thus safety testing by developing better guidelines for implementation by regulatory authorities.

Prof. **Stefan Dübel** (Technical University of Braunschweig, Braunschweig, Germany) presented the phage display method as an alternative to completely replace the use of animals for antibody generation. Antibody phage display allows isolation of fully human antibody fragments from recombinant human antibody gene libraries. Despite the existence of this recombinant replacement method, about half a million animals per year are still used for antibody generation. Polyclonal antibodies derived from animal serum are often not defined with respect to the included antibody specificities, and frequently display unwanted off-target reactivity. Whereas therapeutic antibodies are already produced recombinantly due to their superior quality, the use of recombinant antibodies in diagnostics and research is still rare. Apart from sparing animals, higher quality and specificity of recombinant antibodies should motivate the transition to their use for non-therapeutic applications.

Prof. **Veronika von Messling** (Federal Institute for Vaccines and Biomedicines, Berlin, Germany) spoke about the opportunities and perspectives of alternative methods for licensing and batch testing of medicinal products. The authorization of new vaccines and biomedicines still involves animal experiments at different levels. Many licensed products continue to require testing of every batch before its release, which frequently involves *in vivo* assays. When no function-related test is needed and the detection or quantification of a compound is sufficient, simple standard methods like PCR or ELISA can replace the animal test. A good example is the in-house established method "BINACLE" (binding and cleavage) assay which can, for instance, substitute animal use for safety testing of tetanus vaccines and potency testing of botulinum neurotoxins.

Regulatory approval of an alternative to an animal test requires definition of the relevance and regulatory purpose of the method, its validation, test guideline development, and acceptance. Dr **Sebastian Dunst** (German Federal Institute for Risk Assessment- BfR, Berlin, Germany) presented the process of method development and implementation and pointed out pitfalls that can delay implementation. Problems with reproducibility, predictivity, and relevance of a test are often experienced during the validation phase which can take up to 10 years. Former and current newer validation processes were compared and potential future developments to update the validation process were presented.

Risk assessment and toxicological tests are important for the chemical industry to obtain market approval for new substances. Dr **Barbara Birk** (BASF SE, Ludwigshafen, Germany) presented in-house efforts to validate new approaches and establish alternative methods as well as to gather and assess post-validation data of existent techniques. Alternatives for safety assessment are, for instance, based on regulatory and mechanistic studies as well as on compound screening. The importance of collaborating with regulatory bodies, academia, and other chemical and pharmaceutical companies for the success and rapid implementation of a new method was highlighted and exemplified.

We thank the organizers, especially Dorothea Mühe, the speakers and participants for the pleasant time together as well as for the valuable scientific exchanges on alternatives to animal experimentation.

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Meeting Report

Is There an End in Sight for Animal Testing? Can Organ-on-a-Chip Replace Animal Use in Safety Testing with Advanced Human-focused Approaches?

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The 5th LUSH Prize Conference took place on November 16, 2018 at the *Umweltforum*, Berlin, Germany, ahead of the LUSH Prize 2018 award ceremony. **Rob Harrison**, Director of the LUSH Prize and Editor of Ethical Consumer, welcomed the participants and explained that the mission of the LUSH Prize is to bring forward the date when no further product safety testing in animals is necessary. Reflecting this global issue, past and current winners of the LUSH Prize now represent more than 30 countries.

Ilka Maschmeyer (TissUse, Berlin, Germany) acknowledged that although animal testing is banned for cosmetic products, it is still required for drug development. Although the development of a drug takes on average 13.5 years and costs $2.5 billion, 92% of drugs fail in human clinical trials. To change this, systemic, human cell-based models that better reflect human physiology are urgently needed. The organ-on-a-chip field is now progressing in complexity from 2-4-organ combinations to 10 or more organs to